

RELEASE KINETICS OF MODIFIED PHARMACEUTICAL DOSAGE FORMS: A REVIEW.

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ABSTRACT

Drug release / dissolution from solid dosage forms have been the subject of intense and profitable scientific developments at present times. The release of drug delivery system involves both the process of dissolution and diffusion. In most of the cases the theoretical concepts does not exist and some empirical equations have proved to be more appropriate. Modified drug delivery system such as sustained or controlled release tablets and capsules generally consists of drug dispersed in a polymeric matrix where the process of diffusion predominates. Drug dissolution from solid dosage forms has been described by some kinetic models in which the dissolves amount of drug (Q) is a function of the time (t) or $Q = f(t)$. Mathematical models commonly used to determine the drug release/dissolution profile are Zero order kinetics, First order kinetics, Hixon-Crowell, Higuchi model. Weibull model, Baker-Lonsdale model, Korsmayer-Peppas model and Hopfenberg model. Some other release parameter such as dissolution time, assay time, dissolution efficacy, difference factor (f_1) and similarity factor (f_2) can also used to characterize drug dissolution / release profiles.

KEYWORDS: Drug release kinetics, Modified drug delivery systems, Mathematical models

INTRODUCTION

The quantitative analysis of the values obtained in dissolution /release test is easier when mathematical formulae that express the dissolution results as function of some of the dosage forms characteristics are used.

Zero order kinetics

Dissolution of drug from a dosage form that do not disaggregate and release the drug slowly that is where drug release rate is independent of its concentration can be represented as

$$A_0 - A_t = kt \text{----- (I)}$$

Where A_0 is initial amount of drug in the dosage form; A_t is the amount of drug in the dosage form at time 't' and 'k' is the proportionality constant.

Dividing this equation by A_0 ;

$$1 - (A_t/A_0) = kt/A_0$$

$$\text{or } 1 - A_t/A_0 = k_0 t \text{----- (II)}$$

Where $1 - (A_t/A_0)$ represents the fraction of drug dissolved in time 't' and k_0 the zero order release constant. Graphical representation of fraction of drug dissolved verses time will be linear. This relation can be used to determine the drug dissolution of various types of modified release dosage forms e.g. some transdermal systems, matrix tablets with low soluble drugs (Varles, 1995) coated forms, and osmotic systems etc. The dosage forms following this profile, release the same amount of drug by unit time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

First order kinetics

The first order kinetics was first applied for drug dissolution studies by Gibaldi and Feldman in 1967 (Gibaldi and Feldman, 1970) and later by Wagner in 1969 (Wagner, 1967). In this case the drug release rate is concentration dependent; that can be depicted in decimal logarithm as

$$\text{Log } A_t = \text{Log}A_0 + K_1t/2.303 \text{----- (III)}$$

Where A_t is the amount of drug released in time 't', A_0 is the initial amount of the drug in the solution and k_1 is the first order release constant. Here the graphical representation of the decimal logarithm of drug released verses time will be linear. Example: The dosage form follows this profile such as those containing water soluble drug in a porous matrices (Mulye and Turko, 1995) release the drug that is proportional to the amount of drug released by unit time diminish.

Hixon – Crowell model

To evaluate the drug release with changes in the surface area and the diameter of the particles /tablets, Hixon-Crowell in 1931 (Hixon and Crowell, 1931) recognized that the particle regular area is proportional to the cubic root of its volume, desired an equation as

$$A_0^{1/3} - A_t^{1/3} = k_s t \text{----- (IV)}$$

Where A_0 is the initial amount of drug in the dosage form, A_t is the remaining amount of drug in the dosage form at time 't' and k_s is a constant incorporating the surface volume relation. Example: Tablets where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionality in such a manner that the initial geometrical form keeps constant all the time. Here a graphical representation of the cubic root of the unreleased fraction of the drug verses time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the dosage form diminishes proportionally overtime. This model is used by assuming that release rate is limited by the drug particles dissolution rate and not by the diffusion.

Higuchi model

Higuchi in 1961 (Higuchi 1961) and in 1963 (Higuchi 1963) developed models to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices. To study the dissolution from a planer system having a homogeneous matrix the relation obtained was;

$$A = [D (2C - C_s) C_s t]^{1/2} \text{----- (V)}$$

Where A is the amount of drug released in time 't' per unit area, C is the initial drug concentration, C_s is the drug solubility in the matrix media and D is the diffusivity of drug molecules in the matrix substance. Example: Dissolution of drug in suspension from ointment bases can be depicted by using this relation.

To study the dissolution from a planer a spherical heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the relation obtained:

$$A = D\varepsilon/\tau (2C - \varepsilon C_s) C_s t \text{----- (VI)}$$

Where A, D, C, C_s and t has the same meaning as in equation (V), ε is the matrix porosity, τ is the tortuosity factor of the capillary system.

In general way Higuchi model can be simplified (generally known as the simplified Higuchi model) as,

$$A = K_H t^{1/2} \text{----- (VII)}$$

Where K_H is the Higuchi dissolution constant. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. Example: Drug dissolution from some modified release dosage forms as in

case of some transdermal systems (Costa *et al*, 1996) and matrix tablets with water soluble drugs (Desai *et al*, 1966a and Desai *et al*, 1966b) follows the above relationship as described in equation (VII).

Weibull model

A general empirical equation described by Weibull in 1951 was adopted to the dissolution/release process (Langenbucker, 1972). When applied to drug dissolution or release from dosage forms, the Weibull equation expresses the accumulated fraction of drug 'm' in solution at time 't' by

$$m = 1 - \exp \left[-\{(t-T_i)^b\}/a \right] \text{-----(VIII)}$$

Where 'a' is the scale parameter defines the time scale of the process. T_i is the location parameter, represents the lag time before the onset of the dissolution or release process and in most of the cases will be zero. The shape parameter, b, characterizes the curves as either exponential ($b=1$), S-shaped ($b>1$) or parabolic ($b<1$) (Costa and Lobo, 2003), the equation (VIII) can be rearranged as:

$$\text{Log} [\ln - (1-m)] = b \text{Log} (t-T_i) - \text{log } a \text{----- (IX)}$$

Graphical representation of $\log [-\ln (1-m)]$ verses time 't' gives a linear relation. Shape parameter (b) is obtained from the shape of the line and the scale parameter (a) can be estimated from the ordinate value (1/a) at time $t=1$. This is an empiric model, not deduced from any kinetic fundament, so presents certain deficiencies e.g. it is of limited use of establishing in vivo / in vitro correlation (Christensen, 1983).

Baker-Lonsdale model

In 1974 Baker-Lonsdale (Baker and Lonsdale, 1974) developed the model from the Higuchi model and describes the controlled release of drug from a spherical matrix that can be represented as:

$$3/2 [1 - (1 - A_t/A_\infty)^{2/3}] - A_t/A_\infty = (3D_m C_{ms}) / (r_0^2 C_0) \times t \text{----- (X)}$$

Where A_t is the amount of drug released at time 't' and A_∞ is the amount of drug released at an infinite time, D_m is the diffusion coefficient, C_{ms} is the drug solubility in the matrix, r_0 is the radius of the spherical matrix and C_0 is the initial concentration of the drug in the matrix.

Here graphical representation of the left side of the equation verses time will be linear if the established conditions were fulfilled and Baker-Lonsdale model could be redefined as:

$$3/2 [1 - (1 - A_t/A_\infty)^{2/3}] - A_t/A_\infty = kt \text{----- (XI)}$$

Where 'k' is the release constant corresponds to the slope. The equation (XI) can be used to the linearization of the release data from several formulations of microcapsules. (Shukla and Price, 1989 and Shukla and Price, 1991)

Korsmeyer-Peppas model

In 1983 Korsmeyer *et al*. (Korsmeyer *et al*, 1983) developed a simple, semi-empiric model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t).

$$A_t/A_\infty = at^n \text{----- (XII)}$$

Where 'a' is the constant incorporating structural and geometrical characteristic of the dosage form, n is the release exponent, indicative of the drug release mechanism and the function of 't' is A_t/A_∞ (fractional release of drug).

In 1985 Peppas (Peppas, 1985) used this n value in order to characterize different release mechanism concluding for values for a slab, of $n = 0.5$ for Fickian Diffusion, between 0.5 and 1.0 or $n = 1.0$, for mass transfer following a non-fickian model. $0.5 < n < 1.0$, for anomalous transport. To determine the exponent 'n' the position of the release curve where $A_t/A_\infty < 0.6$ should only be used. This model is generally used to analyze the release of polymeric

dosage form, where the release mechanism is not well known or when more than one type of release phenomenon could be involved.

When there is the possibility of a burst effect, the equation (XII) becomes (Kim and Fassihi, 1997)

$$A_t/A_\infty = at^n + b \text{----- (XIII)}$$

Where 'b' is the burst effect. The Korsmeyer equation i.e. equation (XII) were considered inappropriate since the introduction of the lag period was essential to describe the accurately the quantity of drug released.

An equation
$$A_t/A_\infty = [k(t-l)^n + k'(t-l)^{2n}] \text{----- (XIV)}$$

incorporating a lag period (l), kinetic constant (k and k') for diffusion and erosion controlled release and a diffusional exponent (n) produced the best fit of the data. The kinetic constants were not normally additive, k' becoming increasingly negative with increase in temperature (Ford *et al*, 1991)

Power law

A more comprehensive, but still very simple, semi-empirical equation to describe drug release from polymeric system is the so called power law.

$$A_t/A_\infty = kt^n \text{----- (XV)}$$

Where A_t and A_∞ are the absolute cumulative amount of drug released at time 't' and at infinite time respectively, 'k' is a constant incorporating structural and geometric characteristics of the device and 'n' is the release exponent, indicative of the drug release mechanism.

In equation (XV) when the exponent 'n' takes the value of 1.0, the case corresponds to the zero-order kinetics. For slabs, the mechanism that creates the zero-order release is known among polymer scientist as case-II transport. Here the relaxation process of the macromolecules occurring upon water inhibition into the system is the rate controlling step. Equation (XV) has two distinct physical realistic meanings in the special cases of $n = 0.5$ (indicating diffusion controlled drug release) and $n = 1.0$ (indicating swelling controlled drug release). Values of 'n' between 0.5 and 1.0 can be regarded as an indicator for the super position of both phenomena (anomalous transport). The extreme value for the exponent n, 0.5 and 1.0 are only valid for slab geometry (Siepmann, 2001)

Hopfenberg Model

In 1976 (Hopfenberg, 1976) and in 1997 (Katzhendler *et al*, 1997), developed a general mathematical equation describing drug release from slabs, spheres and infinite cylinders displaying heterogeneous erosions as:

$$A_t/A_\infty = 1 - [1 - k_0 t / C_0 a_0]^n \text{----- (XVI)}$$

Where A_t is the amount of drug dissolved in time 't', A_∞ is the total amount of drug dissolved when the dosage form is exhausted, A_t/A_∞ is the fraction of drug dissolved, k_0 is the erosion rate constant, C_0 is the initial concentration of drug in the matrix and a_0 is the initial radius for sphere or cylinder or the half-thickness for a slab. The value of 'n' is 1, 2, and 3 for a slab, cylinder and sphere respectively.

CONCLUSIONS

The release models with major applications and best describing drug release phenomenon are the Higuchi model, zero order kinetics, Weibull model and Korsmeyer-Peppas model. The Higuchi and zero order models represent two limit cases in the transport and drug release phenomena and the Korsmeyer-Peppas model can be a decision parameter between these two models. While the Higuchi model had a large application in polymeric matrix systems, the zero order models becomes the ideal to describe coated dosage forms or membrane controlled dosage forms.

The criterion to choose the best model to study the drug dissolution/release phenomenon is the use of the coefficient of determination (R^2), to assess the fit of a model equation. Usually, this value tends to get greater with the addition

of more parameters, irrespective of the significance of the variable model. When comparing models with different numbers of parameters, the adjusted coefficient of determination (R^2_{adjusted}) is more appropriate:

$$R^2_{\text{adjusted}} = 1 - [(n-1) / (n-p)] \times (1-R^2) \text{ ----- (XVII)}$$

Where 'n' is the number of dissolution data points and 'p' is the number of parameters in the model. R^2_{adjusted} can actually decrease whereas R^2 always increases or at least stays constant when adding new model parameters thus indicates whether the new parameter really improves the model or might lead to over fitting. It is concluded that the 'best' model would be the one with the highest value of adjusted coefficient of determination.

Along with the coefficient of determination (R^2) or the adjusted coefficient of determination (R^2_{adjusted}), the correlation coefficient (R), the sum of squares of residues (SSR), the mean square error (MSE) and F-ratio probability are also used to test the applicability of the release models.

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